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Center for Drug Evaluation and Research

Advisory Committee for Pharmaceutical Science

and

Clinical Pharmacology

April 13, 2010

Food and Drug Administration

Meeting of the Advisory Committee for Pharmaceutical Science

and

Clinical Pharmacology

April 13, 2010

BRIEFING INFORMATION

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MEMORANDUM

TO: Members, ACPS-CP

FROM: Helen Winkle
Director, Office of Pharmaceutical Science, CDER, FDA

DATE: March 18, 2010

RE: ACPS-CP Meeting April 13, 2010

Dear Committee Members and Invited Guests,

We look forward to your participation in the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP) meeting on April 13, 2010. There will also be a meeting of the committee on April 14th, which will be handled by a separate background package of information.

As you know, the Office of Pharmaceutical Science (OPS) main function is to review the quality of pharmaceutical products prior to market and to monitor changes in manufacturing throughout the life of the products. This includes all pharmaceutical products – small molecule and proteins, and generic versions of these products. Through your participation and advice on the advisory committee, we are able to develop our standards for reviewing and approving products and set policy for regulatory decision-making. The topics to be discussed at our meetings this week are a continuation of our efforts to move forward on important policy matters in the ever changing world of pharmaceutical manufacturing, and principally, to solicit your recommendations, to assist us in this process of sound decision making.

At the start of the meeting, I will outline the goals and objectives for our meeting.

The meeting on April 13th will focus on two bioequivalence (BE) topics relevant to generic drug approval: (1) revising the BE approaches for critical dose drugs, and (2) the use of partial area under the curve (AUC) for the evaluation of abbreviated new drug applications (ANDAs) for products with complex pharmacokinetic profiles.

For the first topic (1), the Office of Generic Drugs (OGD) will discuss the history of BE for critical dose drugs to provide a foundation for your discussions. This will be followed by a presentation on the medical perspectives involving these drugs, and then a presentation on various approaches to demonstrate BE for critical dose (CD) drugs. We will look forward to your input to address the following draft question(s):

Draft Questions for the Committee:

1. Are CD drugs a distinct drug class?
    a. What terminology should be used to delineate this class and how should it be defined?
    b. Should the FDA develop a list of CD drugs?
2. Are the current BE standards sufficient for CD drugs?

   a. Should more rigorous BE standards be adopted?
   b. What should these standards be?
3. Recommendations for future research?

For the second topic (2), we will receive presentations from OGD to frame a discussion on the use of partial area under the curve (AUC) metrics for products with complex pharmacokinetic profiles. We will begin with a topic introduction followed by a presentation by Dr. Kamal Midha on early exposure metrics as a means to demonstrate BE. Prior to your committee discussions, we will then receive presentations on pharmacokinetic profile comparisons and various case studies and approaches to BE. We hope to receive your thoughts focused to the following questions:

Draft Questions for the Committee:

1. Do you endorse FDA's use of partial AUC?
2. Are there other profile comparison metrics that FDA should consider?

You will find appropriate materials on both topics in the background package.

We are looking forward to a very stimulating discussion with the committee on these important topic. We value the opportunity to solicit your assistance in defining and solidifying OPS direction in developing sound, scientific responses to the emerging issues. The meeting will be held at the Hilton Washington D.C./Silver Spring located in Silver Spring, MD. (http://www1.hilton.com/en_US/hi/hotel/DCASSHF-Hilton-Washington-DC-Silver-Spring-Maryland/index.do). If you need any additional information please do not hesitate to contact Bob King (Robert.King@fda.hhs.gov). Have a safe and enjoyable journey to Silver Spring, MD.

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP)

Hilton Washington D.C./Silver Spring
Silver Spring, MD

APRIL 13, 2010

(Scheduled Presentation Times May Change Due to Open Public Hearing Requirements)
TENTATIVE AGENDA
(SUBJECT TO CHANGE)

8:00 a.m. Call to Order and Opening Remarks

Introduction of Committee

Conflict of Interest Statement

8:15 a.m. Welcome and Introductory Remarks

8:45 a.m. ***Topic 1: Revising the Bioequivalence (BE) Approaches for Critical Dose Drugs***

Topic Introduction and Presentations

10:00 a.m. **BREAK**

10:15 a.m. Continued Presentations

10:45 a.m. Topic wrap-up -- Questions to the Committee

11:00 a.m. ***Committee discussions and recommendations***

12:00 p.m. **LUNCH**

1:00 p.m. Open Public Hearing

2:00 p.m. ***Topic 2: Use of Partial Area Under the Curve (AUC) for Products with a Complex Pharmacokinetic (PK) Profile***

Topic Introduction and Presentations

3:00 p.m. **BREAK**

3:15 p.m. Continued Presentations

3:45 p.m. Topic wrap-up -- Questions to the Committee

4:00 p.m. ***Committee discussions and recommendations***

5:00 p.m. **Adjournment**

TOPIC 1:

Revising the Bioequivalence (BE) Approaches for Critical Dose Drugs

Background Information for the FDA Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology

April 13, 2010

Topic: Bioequivalence Criteria of Critical-Dose Drugs

Introduction

Since the passage of the 1984 Drug Price Competition and Patent Term Restoration Amendments to the Food, Drug, and Cosmetic Act, considerable attention has been focused on the approval and use of generic drugs. Generic drug use continues to increase and generic drug availability provides significant cost savings on pharmaceuticals. For example, in 2008, generic drugs accounted for 69% of all prescriptions in the US but less than 16% of total drug spending (1).

Debate continues, however, as to whether the current bioequivalency criteria used to approve generic drugs are appropriate for all drugs, and specifically whether critical-dose (CD) drugs [a] require special consideration. In these drugs with a narrow therapeutic index, small changes in blood concentration have the potential to result in serious therapeutic failures and/or serious adverse drug reactions (2). This has led to ongoing differences of opinion among healthcare providers, scientists, regulatory agencies, pharmaceutical companies, and consumer advocates as to whether critical-dose products should require a greater degree of assurance of similarity to be considered therapeutic equivalents (3).

The following provides a brief summary of the regulatory issues and clinical perspectives related to the interchangeability of CD drugs.

Regulatory Definition

Critical-dose drugs is a designation used in the scientific and professional communities to describe those drugs where comparatively small differences in dose or blood concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or serious adverse drug reactions which may be persistent, irreversible, slowly reversible, or life-threatening events.

A similar term, *narrow therapeutic ratio,* has been defined in the Code of Federal Regulations as follows:

"Evidence that the drug products exhibit a *narrow therapeutic ratio*, e.g., there is less than a 2-fold difference in median lethal dose (LD50) and the median effective dose values (ED50), **-or-** there is less than 2-fold difference in the minimum toxic concentrations (MTC) and minimum effective concentrations (MEC) in the blood." The regulations go on to say that safe and effective uses of these drug products require careful titration and patient monitoring (4).

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[a] A variety of terms are used to describe those drugs in which comparatively small differences in dose or concentration may lead to serious therapeutic failures and or serious adverse drug reactions. These terms include narrow therapeutic index, narrow therapeutic range, narrow therapeutic ratio, narrow therapeutic window, and critical-dose drugs. Critical-dose (CD) drugs and will be used within this document.

The above definition may not be clinically practical, however, in that the values of LD50, ED50, MTC, or MEC are not always available during drug development or even post-approval. The definition, however, emphasizes the importance of careful dosage titration and patient monitoring.

More recently, FDA Guidance for Industry "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations" provided a definition of narrow therapeutic range drug products as follows (5):

"This guidance defines *narrow therapeutic range* drug products as those containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation. Examples include digoxin, lithium, phenytoin, theophylline, and warfarin."

In the past, the agency has developed a working draft list of drug products for which it believed that added quality and inspectional controls may be necessary (6). This list was also used in conjunction with other factors such as drug solubility and permeability to assess the impact of changes made after approval (7). At present, however, the FDA does not formally designate specific critical-dose drugs.

Characteristics of Critical-Dose Drugs

Critical-dose drugs generally have a steep dose/concentration-response relationship. The closeness between effective concentrations and concentrations associated with serious toxicity is characteristic of CD drugs. While most adverse events possess their own dose/concentration-response relationships, some are an extension of therapeutic effects. Due to limitations in clinical studies, however, complete dose/concentration response curves are seldom obtained for a drug product. The degree of adverse events or toxic effects may be judged relative to the severity of the disease under examination. For example, most clinicians will not treat a mild disease at the risk of serious side effects. Yet, one may tolerate more serious side effects to treat a life-threatening disease. Some CD drugs may be given in specialized hospital settings so that the risk/benefit ratio of the drug can be optimized for the patient.

To characterize a CD drug, one may also consider in terms of severity of adverse events and likelihood of their occurrence in the population. For the most part, the severity of adverse events from a CD drug is relatively high and there is a high likelihood of occurrence in the population if the dose is not properly controlled. Accordingly, CD drugs are often subject to therapeutic drug monitoring based on pharmacokinetic (PK) or pharmacodynamic (PD) measures that are predictive of clinical response. For instance,

monitoring of plasma concentration (a PK measure) is critical in achieving the optimal efficacy and safety of theophylline, yet determining prothrombin time (a PD measure) plays an important role in the titration and dose selection of warfarin.

The value of PK or PD monitoring for a CD drug is associated with the degree of variability inherent in the PK or PD measures of the drug. It has been observed that the presence of low within-subject variability in either PK or PD measure is a common feature of CD drugs. Indeed, to be clinically useful, the PK or PD measure chosen for therapeutic monitoring of a CD drug should possess low within-subject variability so that the measure can be used to predict the clinical response of the patient. Conversely, the between-subject variability of the respective PK or PD measure may be relatively high for the drug, and thus therapeutic monitoring is necessary for individualization of dose. In this context, if both PK and PD measures have low within-subject variability, therapeutic monitoring is valuable only with the measure that has large variability between subjects. This can be exemplified by the PD monitoring of warfarin. On the other hand, if there is a PK-PD relationship and between-subject variability is high for PK measures, PK monitoring will be most useful for dose optimization.

The presence of non-linear PK in some drugs, such as phenytoin, can further complicate the predictability of dose-response relationship in the clinical setting. Phenytoin exhibits capacity-limited metabolism (Michaelis-Menten kinetics) over the range of therapeutic doses. For most drugs, the rate of metabolism is well below the upper limit of the enzyme activity at therapeutic concentrations. However, this is not the case for phenytoin. The rate of phenytoin metabolism is close to the limit of its enzyme activity and thus it is saturable at therapeutic concentrations. As a consequence, there is a disproportionate increase in the steady state concentration with dose. A small difference in the bioavailability (or dose) of phenytoin may result in a large difference in the plasma concentration after multiple-dose administration.

Based on the above considerations, examples of CD drugs may include digoxin, disopyramide phosphate, levothyroxine sodium, lithium carbonate, phenytoin sodium, procainamide hydrochloride, quinidine gluconate, quinidine sulfate, theophylline and warfarin sodium. It is noted that PK monitoring has been applied to most of these drugs clinically, with the exception of warfarin sodium and levothyroxine sodium for which therapeutic monitoring is done based on the PD measures, prothrombin time and thyroid-stimulating hormone (TSH) levels and/or free T_4, respectively.

Statistical Criteria for Bioequivalence

Bioequivalent drug products display comparable bioavailability and thus posses an equivalent rate and extent of absorption when studied under similar experimental conditions. The FDA statistical criteria for determining bioequivalence are outlined in the FDA publication, Approved Drug Products with Therapeutic Equivalence Evaluations and have evolved with time and an improved understanding of biostatistics and drug characteristics (8). Bioequivalence studies are used not only when comparing pharmaceutically equivalent generic formulations with innovator products, but also when

significant manufacturing changes are made in a marketed product or when the proposed dosage form in a new drug application has changed from that which was used in pivotal trials (9).

The current two one-sided test procedure was adopted in 1987. This approach is based on the premise that a 20% difference between test and reference product is not clinically significant (10, 11). A typical bioequivalence study is conducted using a two-treatment crossover study design in a limited number of volunteers, generally healthy adults. Two products are deemed bioequivalent if the 90% confidence intervals of the geometric mean test/reference ratios for both Cmax and AUC are entirely within the limits of 80–125% (8, 12).

The two one-sided tests procedure for evaluating BE simultaneously controls the average difference between a test and a reference product, as well as the precision with which the population averages are estimated. The precision is, in turn, determined by the within-subject variability of BE measures and the number of subjects in the study and this will be reflected in the width of the 90% confidence interval. In other words, a drug product with large within-subject variability may need a large number of subjects in order to pass bioequivalence standards, while a product with very low variability may pass with a larger difference in mean response (8).

CD drugs have small within-subject variability, allowing for tight treatment control with individual therapeutic blood monitoring. This low variability has led some to believe that, given the same sample size, the current BE limits may be too wide for certain CD drugs. This is perhaps more worrisome if the CD drug also has saturable metabolism or excretion, or if 2 generic CD drugs are switched at the pharmacy level, a scenario increasingly likely with cost containment strategies. Coupling these factors with a steep dose-response curve with CD drugs which may differentially impact the effects of bioavailability differences on therapeutic outcomes, some advocate a tighter BE limit may be indicated for certain products.

Clinical Evidence

To date, there is no well- controlled and statistically significant clinical study that is able to demonstrate therapeutic failure related to switching between generic and innovator CD drugs although numerous annotated reports exist. The question remains, however, as to whether currently available methods are sensitive enough to discern differences between two drug products if they indeed exist. Spontaneous adverse event reporting systems have several limitations in detecting therapeutic inequivalence. To begin with, the spontaneous adverse drug reaction reporting data are designed to generate a signal or hypothesis that there is a problem with a certain drug and not to compare one drug against another. Well documented biases including the Weber effect and secular trending can complicate comparative analyses (13). In addition, the reporting rate for adverse events varies between drugs and for the same drug over time. At baseline the overall reporting rate is low, with studies estimating that the fraction of reports received by the Agency to vary between 0.3% and 33%, but the percentage for any specific drug is

unknown (14). Finally, health care providers expected to report changes in clinical response may be unaware that formulation switching occurred or may not attribute clinical changes to product switching, further limiting the value in voluntary submissions. Unfortunately, randomized clinical trials are largely impractical to detect therapeutic differences between two products, given the cost and extremely large sample sizes which would be required. The bulk of the data, then, is found in case reports and observational studies which are limited in their ability to prove causality. The absence of firm evidence coupled with questions related to the current metrics has led to ongoing controversy in the medical and scientific communities as to substitutability of CD drugs.

The FDA has conducted several retrospective analyses of bioequivalency studies to quantify the pharmacokinetic differences between generic and innovator products. Most recently, 2070 single-dose clinical bioequivalence studies of drugs approved by the FDA from 1996-2007 were compared. The average difference in Cmax and AUC between generic and innovator products was 4.35% and 3.56%, respectively (12). These results were not unlike those from 2 previous FDA reviews (2, 15), and supports the current BE standards as a whole. It should be noted, however, that CD drugs comprise a small percentage of drug approvals and these studies evaluated the average differences in Cmax and AUC of all drugs approved.

Multiple crossover designed pharmacokinetic studies have also been conducted in patients, comparing Cmax and AUC from different manufacturers. For example, a small, nonblinded, intra-individual trial in 14 adult patients with focal epilepsy was conducted. Patients were receiving monotherapy with innovator sustained-release carbamazepine which was replaced by a generic formulation of the identical strength. The two formulations were found to be bioequivalent with slightly higher bioavailability for the generic formulation (AUC 111.5% [90% confidence interval (CI) 105.6-117.8%]; C-max 110.1% [90% CI 100.4-117.0%]). Adverse events were common following the switch to generic, with 1 patient dropping out of the study and 8 of the 13 remaining participants experiencing adverse events (dizziness, nausea, ataxia, diplopia and nystagmus) (17). A recent study was completed in Denmark comparing steady state pharmacokinetic parameters before and after formulation switch in 9 seizure patients on chronic lamotrigine and who previously reported problems. Five of nine patients had PK deviations beyond +/- 10%, the BE requirement for lamotrigine in Denmark, but largely within the US standard of 80-120%. Three of these patients had deviations in several parameters which were consistent with their original complaint (i.e. complaint of ataxia corresponding with Cmax +21% and breakthrough seizures corresponding with Cmax -15%) (16). Limitations of these study designs included their small size, lack of control group, and unblinded design.

Few prospective studies in the literature exist evaluating clinical endpoints of CD generic formulations with innovator products in patient populations. Several small prospective studies have also sought to compare generic and brand name warfarin with respect to clinical end points such as INR, frequency of adverse events, and number of required dose adjustments and found no significant differences (18-21). The results of these

studies should be considered in the context of their size and definitive conclusions would require larger patient populations.

In contrast to the limited number of prospective studies, numerous published case reports and retrospective chart reviews describe a loss of efficacy and/or adverse events temporally related to switching from innovator to generic CD products (22-25). For example, a retrospective review of 200+ medical records of seizure patients identified 8 patients who had increased frequency of seizures following generic phenytoin substitution for Dilantin. The mean total phenytoin serum concentration on brand was 17.7 +/- 5.3 mg/L, decreased to 12.5 +/- 2.7 mg/L on generic, increased to 17.8 +/- 3.9 mg/L after reintroduction of brand (22). Limitations of this and other similar studies included a small sample size, lack of control group and retrospective design. A more recently published retrospective case-control study of epilepsy patients compared 991 patients who experienced an epileptic event with 2973 controls. Among the patients who experienced a seizure, 11% had undergone an A-rated AED substitution, compared with 6.3% of the control group (odds ratio 1.84, 95% confidence interval 1.44–2.36). Thus, in this case-control analysis, patients who had an epileptic event were about 80% more likely than matched controls to have recently had an AED substitution (26). While case reports and retrospective studies cannot prove causality, they have led many in the medical community to question the equivalence of generic CD products.

Public and Health Care Provider Perception

A 2001 article in the Journal of the American Pharmacists Association found a variety of concerns across pharmacy groups related to the generic substitution of narrow therapeutic index drugs (27). The products that consistently topped pharmacists' lists of poor candidates for substitution were warfarin, phenytoin, and digoxin. Pharmacists were also particularly hesitant to substitute generics for carbamazepine, levothyroxine, furosemide, and procainamide (27). In a small survey of 59 transplant pharmacists in 1997, only 12% of the respondents said they thought that the FDA guidelines on bioequivalence testing were appropriate for drugs with a narrow therapeutic index (NTI), and 92% thought that bioequivalence testing for NTI drugs should be conducted in actual patients. 95% of respondents expressed a belief that generic products of some critical-dose drugs should not be dispensed (28).

Many physicians and patients perceive that generic CD drugs are not always equivalent to the innovator product. A recent survey looked at physician and patient perceptions related to generic antiepileptic drugs. 550 adult patients with self-reported epilepsy and 606 physicians caring for patients with the disease responded to the survey, and the results highlight continued concerns about the safety and efficacy of generic substitution of antiepilepsy drugs (AEDs). For example, 88% of physicians were concerned about an increase in breakthrough seizures in patients switched from brand to generic or between generics, and 65% indicated they cared for a patient who experienced a breakthrough seizure likely as a result of formulation switching to generic. Similarly, 65% of patients were concerned about the efficacy of generic AEDs. Physician opinions on generic AEDs were reflected in their prescribing behaviors, with respondents reporting that 55%

of their AED prescriptions for epilepsy were written for brand only (29). A survey of 130 electrophysiologists about experiences with generic antiarrhythmic drugs elicited 64 responses, of which 33 reported one or more adverse events temporally associated with formulation substitution. Fifteen of the respondents indicated they write "dispense as written" on all antiarrhythmic prescriptions, while the majority stated they sometimes allow generic substitution and often experience financial pressure to do so (24).

Importantly, these opinions appear to be based on little awareness of the generic approval process. Multiple surveys have confirmed a general lack of understanding of bioequivalency standards among the medical community with only 17% of physicians correctly identifying the FDA standards for bioequivalence (30). Furthermore, it is likely that far fewer of these respondents are aware that bioequivalency extends beyond the scope of generic drugs and impacts innovator products as well. These and other surveys underscore the current disconnect between the current FDA stance on CD drugs and the opinions of some in the medical community.

Medical Association Policies and Legislation

The American Medical Association (AMA) issued a report in 2007 generally supporting the use of generic drugs and recognizing the potential cost savings with their use. The report went on to state, however, that physicians should report serious adverse events that may be related to generic substitution, and that the FDA should investigate ways to more effectively inform physicians about the bioequivalence of generic drugs, as well as the approach used to determine individual product bioequivalence. In addition, the FDA should fund or conduct additional research evaluating the optimum methodology to determine bioequivalence between pharmaceutically equivalent drug products. Finally, the AMA has a specific policy directive (D-125.991) that urges the FDA to re-examine its bioequivalence standards for levothyroxine (31).

Physician specialty associations have also made official statements related to CD drugs. For example, a 2006 position statement from the American Academy of Neurology opposes generic substitution of anticonvulsant drugs for the treatment of epilepsy without the attending physician's approval and opposes prior authorization requirements by public and private formularies for anticonvulsant drugs in the treatment of epilepsy (32). A 2006 joint position statement from the American Association of Clinical Endocrinologists, The Endocrine Society, and the American Thyroid raises concerns with the FDA's current procedure for evaluating bioequivalence for generic levothyroxine products and recommends that physicians not substitute levothyroxine drug products (33). A 2003 published Report of the AST Conference on the use of Immunosuppressive Drugs and Generic Immunosuppressants included support of the use of generic CD immunosuppressive agents to low-risk transplant recipients with appropriate therapeutic blood monitoring. The report held, however, that currently there are insufficient data to make separate recommendations regarding the use of generic immunosuppressant medications in potentially at-risk patient populations, (e.g., African Americans and pediatrics). It went on to recommend that demonstrations of bioequivalence in at-risk patient populations should be incorporated into the generic drug approval process (34). A

long term goal of the AST Community of Practice for Transplant Pharmacists Executive Committee 2009-2010 includes working with the AST and other transplant organizations to lobby for changes in the FDA generic approval process for narrow therapeutic index drugs (35).

Finally, states have the ability to enact specific legislation related to CD substitution, but the policies are inconsistent across the US. Thirteen states currently list specific narrow therapeutic range drugs which are considered nonsubstitutable (27, 36). For example, the pharmacy laws of North Carolina require that "A prescription for a narrow therapeutic index drug shall be refilled using only the same drug product by the same manufacturer that the pharmacist last dispensed under the prescription, unless the prescriber is notified by the pharmacist prior to the dispensing of another manufacturer's product, and the prescriber and the patient give documented consent to the dispensing of the other manufacturer's product"(37). Multiple other states currently have mandatory generic substitution laws, though these laws may vary significantly. In Oklahoma, a pharmacist must obtain approval from the patient or prescriber before substituting with a generic product, however, Vermont requires a physician provide a statement of generic ineffectiveness in order to prevent generic substitution (27, 36).

Current Regulatory Approaches

Canada:

Health Canada has long recognized a category of drugs which required greater degree of assurance in bioequivalency studies. A 1992 Report prepared by the Expert Advisory Committee on Bioavailability specifically looked at drugs having complicated or variable pharmacokinetics. The report recognized narrow therapeutic range and highly toxic drugs and went on to set the following bioequivalency standards for these two drug categories. The 95% confidence interval of the relative mean AUC (and relative mean Cmax) of the test to reference formulation should be within 80 to 125%. Studies should be performed in both the fed and fasting state (38).

In 2006, Health Canada released new guidance which created a new category of *critical dose drugs* intended to replace the categories of narrow therapeutic range drugs and highly toxic drugs from the 1992 report. *Critical dose drugs* are those drugs where comparatively small differences in dose or concentration lead to dose-and concentration-dependent, serious therapeutic failures and/or serious adverse drug reactions which may be persistent, irreversible, slowly reversible, or life threatening, which could result in inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or death. Drugs currently designated as having a critical dose are: cyclosporine, digoxin, flecainide, lithium, phenytoin, sirolimus, tacrolimus, theophylline, and warfarin (39).

Since small differences in the amount of a *critical dose drug* available to the body may result in consequences more serious than with "uncomplicated" drugs, the required

degree of assurance of the similarity of reference and subsequent-entry products is greater than with "uncomplicated" drugs (39).

For *critical dose drugs*, the **90%** confidence interval of the relative mean AUC of the test to reference formulation should be within **90.0 to 112.0%;** the relevant AUC or AUCs as described in Guidelines A and B are to be determined. These conditions are to be met in both a fed and fasted state (39). While the level of confidence was changed from 95% (1992) to 90%, the confidence interval for AUC was narrowed to 90-112%, representing a meaningful tightening of the standard. (40).

Europe:

European draft guidance states that "in specific cases of products with a narrow therapeutic index, the acceptance interval may need to be tightened." The guidance goes on to describe CD drugs as having steep concentration response relationships for efficacy and/or toxicity and generally requiring individualized dosing based on plasma concentration monitoring. Identifying CD drugs and determining the need for narrowing the BE acceptance intervals should be determined on a case by case basis. Finally, the acceptance interval for concluding bioequivalence for CD products should generally be narrowed to 90-111% (41).

Certain countries within the European Union have more specific policies and guidance related to narrow therapeutic index drugs. For example, the Danish Medicines Agency may grant approval of drugs with a narrow therapeutic index passing the usual acceptance limits (80-125%), but the bioequivalence acceptance limits must lie within 90-111% for automatic substitution to be considered. These drugs include aminophylline, theophylline, lithum, thyroxine, warfarin, antiepileptic agents, antiarrhythmics, and tricyclic antidepressants. Immunosuppressive agents bioequivalence acceptance limits must always lie within 90-111% range for authorization. (42)

US (FDA):

Current FDA policy maintains the traditional bioequivalence limits (80-125%) for all drug products, including those with a narrow therapeutic index. The FDA Guidance for Industry "*Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations*" adds a recommendation that sponsors consider additional testing and/or controls to ensure the quality of drug products containing narrow therapeutic range drugs. The approach is designed to provide increased assurance of interchangeability for drug products containing specified narrow therapeutic range drugs (5).

In addition, 21 CFR Sec. 320.33 outlines the criteria and evidence to assess actual or potential bioequivalence problems. These regulations allow some discretion in considering an appropriate BE interval by stating that the Commissioner of Food and Drugs shall consider the following factors, when supported by well-documented evidence, to identify specific pharmaceutical equivalents and pharmaceutical alternatives

that are not or may not be bioequivalent drug products. These factors include: evidence that the drug products exhibit a narrow therapeutic ratio, e.g., there is less than a 2-fold difference in median lethal dose (LD50) and median effective dose (ED50) values, or have less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and safe and effective use of the drug products requires careful dosage titration and patient monitoring. (4) To this point, the agency has not revised the bioequivalence criteria for any specific drug products.

Conclusions

The medical and scientific communities remain divided on the substitutability of generic CD drugs, and the majority of the medical community and patient groups fail to understand the current methodology behind bioequivalence testing or the various applications for which the testing is used.

Some clinicians and scientists question whether the current post marketing system is able to detect clinically significant differences between innovator and generic CD drugs or between different formulations of CD drugs. Good prospective scientific evidence remains elusive, however, and the large scale clinical trials which are perhaps required to assess therapeutic inequivalence are impractical and unlikely to occur in the near future.

Possible strategies to consider in dealing with CD drugs include 1. maintaining the current BE standards for all drug products but increasing education and outreach to the medical community, 2. narrowing the current acceptance limits for AUC, 3. applying scaling approach concepts, or 4. developing individual drug specific guidances as needed.

With this in mind, the Advisory Committee is asked to consider the following questions related to CD drugs products:

1. Are CD drugs a distinct drug class?
    a. What terminology should be used to delineate this class and how should it be defined?
    b. Should the FDA develop a list of CD drugs?
2. Are the current BE standards sufficient for CD drugs?
    a. Should more rigorous BE standards be adopted?
    b. What should these standards be?
3. Recommendations for future research?

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TOPIC 2:

Use of Partial Area Under the Curve (AUC) for Products with a Complex Pharmacokinetic (PK) Profile

Background Information for the FDA Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology

April 13, 2010

Topic: Use of partial area under the curve (AUC) for the evaluation of abbreviated new drug applications (ANDAs) for products with complex pharmacokinetic profiles

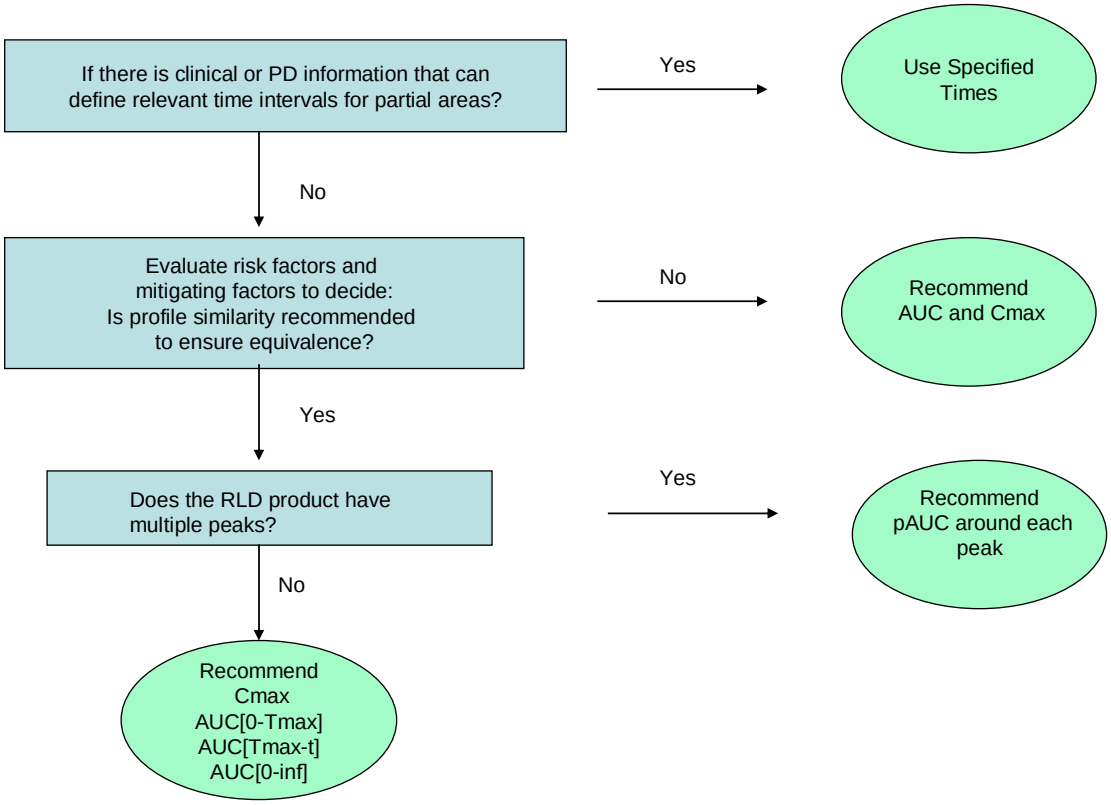
Problem Definition

A generic drug product is deemed to be bioequivalent to its corresponding reference product if the two show no significant difference between the rate and extent of drug availability at the site of action. For systemically active drugs, two products are deemed bioequivalent if the 90% confidence intervals of the geometric mean test/reference ratios for the pharmacokinetic (PK) parameters C_{max} (rate of absorption) and AUC (extent of absorption) fall within the limits of 80-125%. Thus, the metrics traditionally applied to bioequivalence (BE) studies are C_{max}, AUC_{0-t}, and $AUC\infty$. However, the Office of Generic Drugs (OGD) has recently encountered several review examples of multiphasic modified-release (MR) products for which it was concluded that the generic and corresponding reference products may not be therapeutically equivalent (switchable), despite being deemed bioequivalent when the traditional metrics were compared.

Currently, for one drug product[1], FDA asks applicants developing generic products to establish bioequivalence to the reference by comparing partial AUCs over clinically relevant time intervals. FDA's recommendations are released to the public via individual product bioequivalence guidances. The FDA is beginning to apply this approach to other multiphasic MR drug products. Also during the review of such products, T_{max} differences between test and reference products are examined. If test and reference T_{max} values differ markedly, the OGD consults with the relevant CDER clinical division to determine whether these differences may result in a lack of therapeutic equivalence.

OGD would like to develop more general guidelines for determining when additional bioequivalence metrics are needed and which additional metrics are most appropriate for particular products. Thus OGD is in the process of developing a decision tree and would like the committee input on several aspects of the draft decision tree.

Proposed Decision Tree for MR products



For each decision point we would like the committee to consider the following questions.

A. Clinically Relevant Time Intervals

The background contains two examples (Appendix B and C) where FDA has identified clinically relevant time intervals because of a clear link between drug concentration and effect. These time intervals were used to recommend specific partial areas. In both cases, information from approved immediate release (IR) products figured in the evaluation.

Questions for the committee are:

- Are there particular therapeutic categories where there clinically relevant time intervals would generally be expected?
- Is there a general recommendation for the use of the IR T_{max} in selecting a partial area interval?

B. Profile Comparison Methods

If it is determined that it is necessary to apply BE metrics other than C_{max}, AUC_{0-t}, and AUC_{∞}, the next decision point concerns the metrics to ensure profile similarity. In the

case studies (Appendix B and C) FDA has recommended use of partial AUC. Appendix A provides detailed background on partial AUC. Appendix D outlines a literature survey of potential metrics that FDA has also evaluated or is in the process of evaluating.

We would like the committee to consider the following questions

1. Do you endorse FDA's use of partial AUC?
2. Are there other profile comparison metrics that FDA should consider?

Appendix A: Background on Partial AUC

In the Guidance for Industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (March 2003), FDA recommended using partial AUC to assess early exposure in situations calling for more precise control of drug absorption into the systemic circulation:

> For orally administered immediate-release drug products . . . .[a]n early exposure measure may be informative on the basis of appropriate clinical efficacy/safety trials and/or pharmacokinetic/pharmacodynamic studies that call for better control of drug absorption into the systemic circulation (e.g., to ensure rapid onset of an analgesic effect or to avoid an excessive hypotensive action of an antihypertensive). In this setting, the guidance recommends use of partial AUC [AUC_{pR}] as an early exposure measure.[2]

The guidance recommended that the partial area be truncated at the population median of T_{max} value observed for the reference formulation **in the study**. The discussion of this concept in the guidance and the supporting literature primarily focused on immediate release products for which there was an expectation of immediate onset of a pharmacological effect.

In this background material and in other discussions, we define the partial AUC as the area under the plasma concentration profile calculated between two specified time points. This is a generalization of the concept presented in the 2003 guidance and early literature which used partial AUC to refer to AUC(0-T_{max}[reference product]) or the partial AUC to the reference product T_{max}.

For an early exposure metric of a multiphasic MR product, there are several proposed methods of identifying the upper time limit (the lower time limit is zero), as follows:

- The reference product T_{max} observed in the study;
- A pre-specified upper limit based on the clinically relevant time for the drug effect;
- The T_{max} of an approved IR formulation; or
- The T_{max} of an approved IR formulation plus 2 standard deviations.

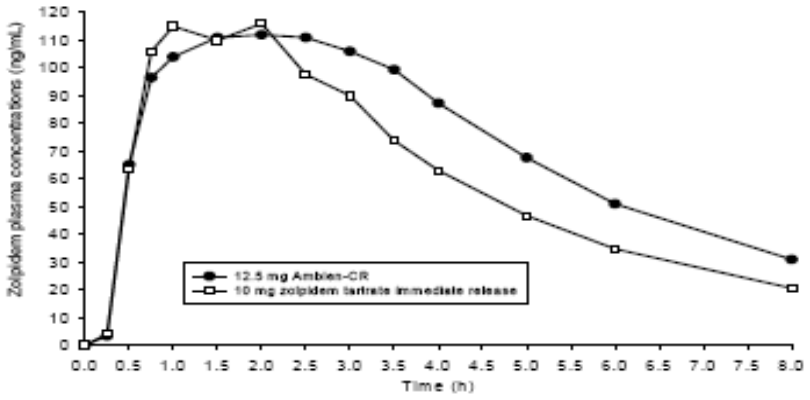
The use of the T_{max} of an IR formulation is motivated by the existence of multiphasic products which contain IR and extended-release (ER) components and the IR component is intended to give similar onset of effects as an approved IR product.

The partial AUC concept may also be applied to time intervals that are not related to early exposure. For example, a partial $AUC_{8\text{-}16}$ could be proposed if there were a need to ensure equivalent drug exposure over that time interval.

Appendix B: Partial AUC Metrics for Generics to Zolpidem MR Tablets

The IR tablet Ambien® (zolpidem tartrate) was approved in the US in 1993 and is marketed for the short-term treatment of insomnia[3]. The active ingredient in Ambien® is the hypnotic agent zolpidem. Ambien CR®, a multiphasic MR formulation, was approved in 2005[4]. Ambien CR® consists of a coated two-layer tablet: one layer that releases its drug content immediately and another layer that allows a slower release of additional drug content. Ambien CR® exhibits biphasic absorption characteristics, which results in rapid initial absorption from the gastrointestinal tract similar to zolpidem tartrate IR, then provides extended plasma concentrations beyond three hours after administration. Thus, in the first IR phase, Ambien CR® is designed to provide initial plasma concentrations comparable to IR zolpidem tartrate. In the second, sustained release phase, Ambien CR® is designed to maintain plasma concentrations of the drug during the middle of the night, and retain a low potential for next-day residual effects such as pyschomotor impairment[5].

By contrast with IR Ambien®, which is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation[6]. Ambien CR® is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset) [7]. The FDA-approved label also states that Ambien® CR has no residual effects when used as directed. This finding is supported by five clinical studies [three controlled studies in adults (18-64 years of age) and two controlled studies in the elderly (≥ 65 years of age)] showing no effect on vigilance, memory, or motor function eight hours after a nighttime dose. In addition, no evidence of next-day residual effects was detected with Ambien CR® using self-ratings of sedation. The figure below, taken from the Ambien CR® label, compares plasma concentration-versus-time profiles in subjects receiving single doses of either zolpidem tartrate IR tablets or Ambien CR®.



The OGD undertook an investigation to determine (1) whether AUC and C_{max} alone were sufficient to ensure that generic versions would be therapeutically equivalent to Ambien CR®; and (2) to propose additional BE metrics, if needed. The investigation included a review of the scientific literature and regulatory submissions to the FDA. Interpretation

of existing data required modeling and simulation to reconstruct plasma concentration profiles for investigational formulations. The analysis focused on the following information:

- Ambien® and Ambien CR® produce equivalent sleep onset;
- Ambien CR® produces improved sleep maintenance relative to Ambien®; and
- Patients taking Ambien CR® show a lack of residual effects.

The endpoints used to measure sleep onset in Ambien CR®clinical trials included objective measures (polysomnography recordings) of sleep induction (by decreasing latency to persistent sleep [LPS]) and patient-reported global impression regarding the aid to sleep. As these clinical endpoints can be measured over relatively short time intervals, they were used to attempt to characterize the pharmacodynamic / pharmacokinetic (PK / PD) relationships between time to sleep induction and zolpidem plasma concentrations.

Using zolpidem in vitro-in vivo correlation (IVIVC) and clinical / PD data submitted to the Agency, zolpidem PK profiles were estimated using IVIVC, deconvolution, and simulation approaches. The consensus of the different approaches was that $AUC_{0\text{-}1.5h}$ was best at discriminating between formulations with respect to sleep onset. This finding is supported by clinical data that supported the approval of Ambien CR®, showing that at least 90% of subjects on active treatment were asleep 1.5 hours after dosing. Notably, both Ambien® and Ambien CR® have very similar drug absorption over this time period. However, it was not possible to establish a zolpidem therapeutic concentration range that would ensure equivalent sleep onset.

We conclude that the interval from dosing to 1.5 hours post-dosing is the time that most subjects receiving Ambien® fall asleep. In addition, for both Ambien® and Ambien® CR, this is the time interval where there is the biggest difference between the rate of falling asleep between drug and placebo. At later times (2 hours) all patients are asleep, whereas at earlier times (such as 1 hour), there is still a growing difference in the rate of falling asleep compared to placebo. Therefore, equivalence in $AUC_{0\text{-}1.5h}$ will ensure that generic products have similar initial exposure to both Ambien® and Ambien CR® over this interval.

The variability of $AUC_{0\text{-}1.5h}$ is higher than that of C_{max}, $AUC_{0\text{-}t}$, and $AUC\infty$, but reasonable for use in an equivalence test. In-house data suggested that the within-subject variability of the zolpidem $AUC_{0\text{-}1.5h}$ following Ambien CR® dosing ranged from 20-60%. Simulated power curves suggest that a two-way crossover BE study might need to enroll as many as 100 subjects to determine whether two products are bioequivalent at 80% power. The number of study subjects can be reduced by using alternative approaches, such as replicated study designs for reference-scaled average BE analysis, or sequential study designs.

We also recommend using $AUC_{1.5h\text{-}t}$ as a BE metric rather than $AUC_{0\text{-}t}$. If a proposed generic and the corresponding reference Ambien CR® produce the same exposure over

this time interval, it is reasonable to assume that they will be therapeutically equivalent with respect to sleep maintenance and lack of residual effects upon waking (8 hours after dosing). OGD's simulations showed that $AUC_{0\text{-}1.5h}$ was the BE metric most sensitive to changes in the in vivo release from the formulation. In addition, none of the clinical data reviewed suggested that zolpidem plasma concentration ratios that are within the 80-125% BE limits ensured by equivalence in $AUC_{0\text{-}1.5h}$, $AUC_{1.5h\text{-}t}$, $AUC\infty$, and C_{max} will have a significant effect on residual effects.

Finally, we recommend that the traditional metrics of $AUC_{0\text{-}t}$, $AUC\infty$, and C_{max} are sufficient to establish BE in the fed state. Food delays the absorption of the RLD, with the label stating that for earlier sleep onset Ambien CR® should not be administered with or immediately following a meal. The delay due to food eliminates the need for an additional measure of early exposure.

The above proposals were presented to and received concurrence from CDER's Division of Neurology Products, Division of Clinical Pharmacology I, and Division of Pharmacometrics.

Appendix C: Partial AUC Metrics for Generics to MR Methylphenidate Products

Ritalin® (the methylphenidate HCl IR tablet), approved in 1955,[8] is indicated for the treatment of attention deficit disorder (ADD).[9] Methylphenidate releases and inhibits uptake of catecholamines (primarily dopamine), and the resulting increase in these neurotransmitters is considered to be the basis for its clinical activity.[10] Within 1-2 hours after oral administration of a clinical dose of methylphenidate, peak serum concentration is achieved and maximum clinical effects are manifested.[11] Methylphenidate has a short plasma half-life (2 hours) and an equally short duration of efficacy of 2-3 hours. Thus, the IR formulation is given tid or bid.

In 1982, Ritalin-SR®, a sustained-release (SR) formulation of methylphenidate HCl, was approved.[12] The Ritalin-SR® label states that it can be used in place of Ritalin® when the 8-hour dosage of Ritalin-SR® corresponds to the titrated 8-hour dosage of Ritalin®.[13] However, the SR methylphenidate HCl formulations are widely believed to be not as effective as multiple doses of the IR formulations, because sustained methylphenidate levels may lead to the development of acute tolerance.[14] [15]

Concerns that traditional methylphenidate HCl SR formulations could not provide coverage throughout the day led to the development of multiphasic MR methylphenidate HCl products. These products are formulated to release a bolus of methylphenidate HCl, followed by sustained delivery later in the day. Three such formulations of methylphenidate HCl are presently marketed: Concerta®, Metadate CD®, and Ritalin LA®. Each of these products is intended to be given once daily, in the morning. According to the FDA-approved labels for these products, clinical studies showed statistically significant improvement in behavioral assessment scores throughout the day following administration of a single morning dose. This is in contrast to the traditional SR methylphenidate HCl formulations, which do not provide coverage throughout the entire day.[16]

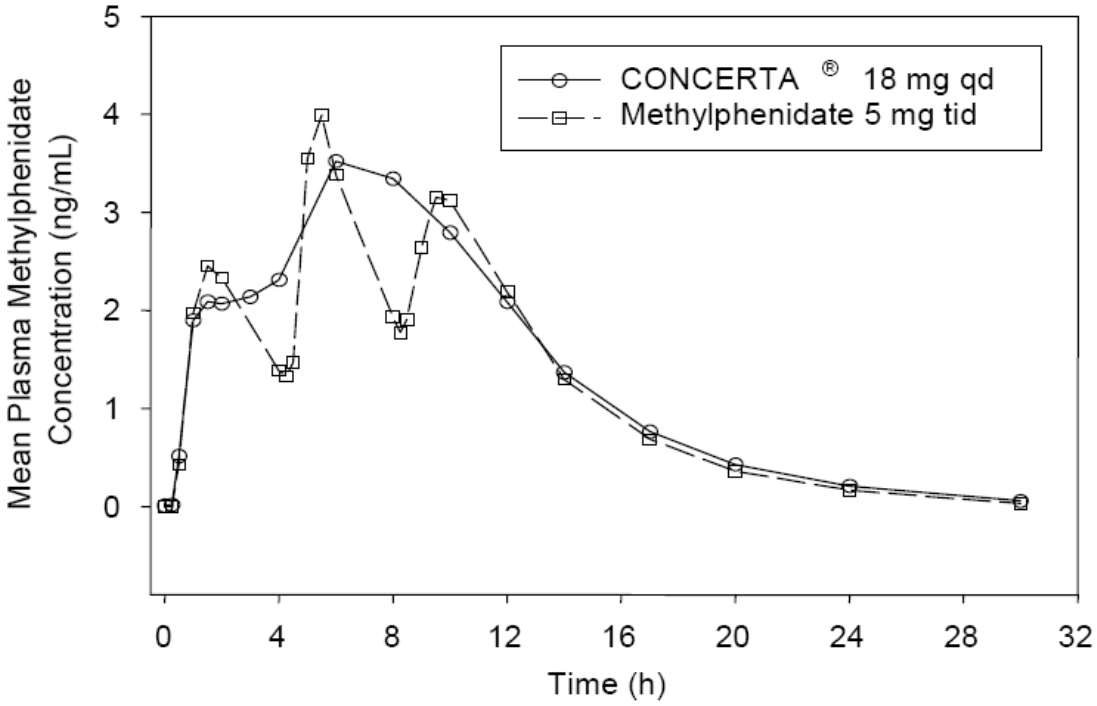
Concerta®, approved in 2000, [17] is a tablet formulation consisting of an ER core with an IR overcoat.[18] Following oral administration of Concerta®, plasma methylphenidate concentrations increase rapidly, reaching an initial maximum at about one hour, followed by gradual ascending concentations over the next 5 to 9 hours, after a graduate decrease begins. The Concerta® label states that the mean methylphenidate T_{max} across all doses ranged from 6-10 hours.

Metadate CD®, approved in 2001,[19] is formulated as IR and ER beads such that 30% of the dose is provided by the IR component and 70% of the dose is provided by the ER component.[20] Metadate CD® has a plasma/time concentration profile showing two phases of drug release with a sharp, initial slope similar to a methylphenidate IR tablet, and a second rising portion approximately three hours later, followed by a gradual decline. According to the labeling, a single dose in the morning achieves a median peak concentration about 1.5 hours after dosing, followed by a second peak concentration about 4.5 hours after dosing.

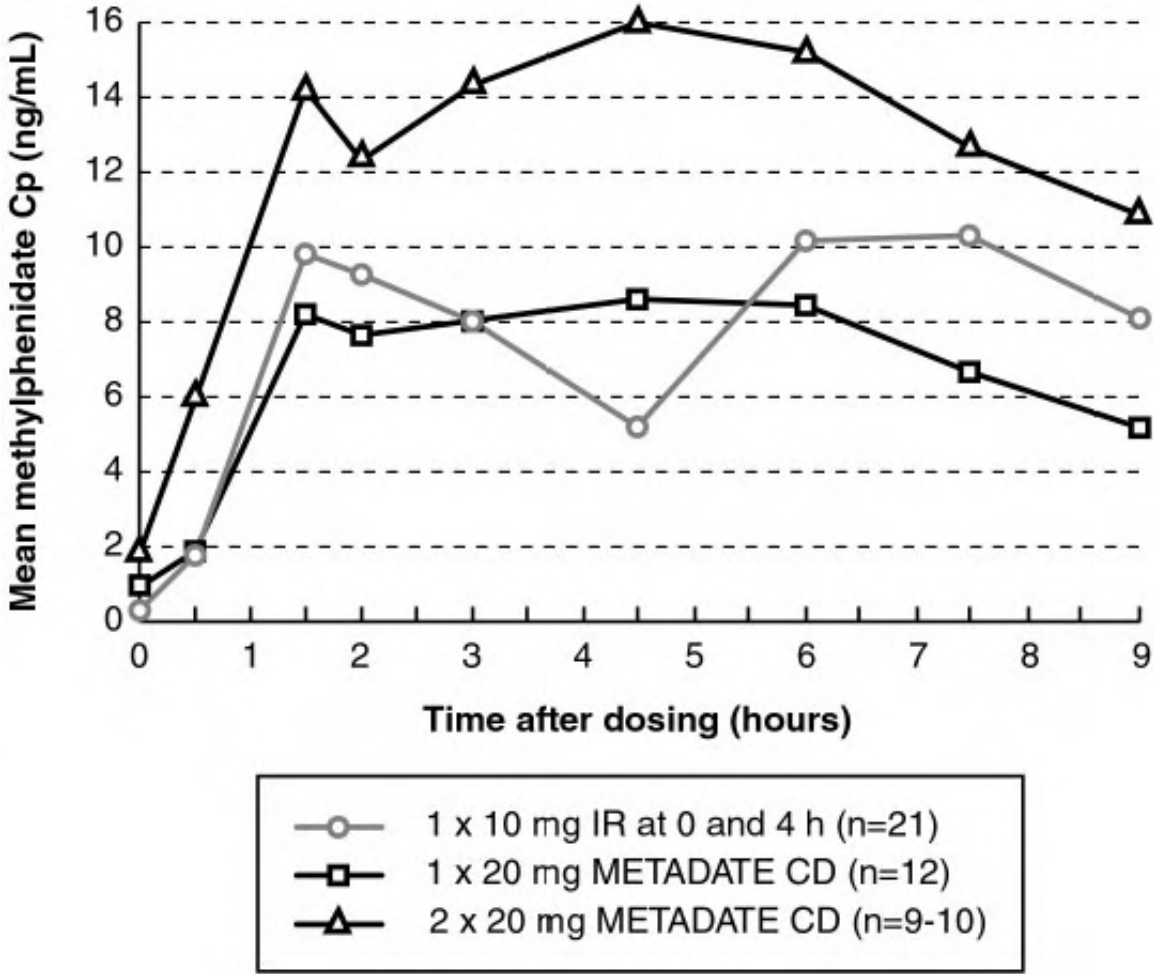
Ritalin LA® was approved in 2002.[21] The Ritalin LA capsule contains half the dose as IR beads and half as enteric-coated, delayed-release (DR) beads, thus providing an IR release of methylphenidate and a second DR of methylphenidate, resulting in a bi-modal release profile.[22] The labeling states that the following a single dose of this product, a first T_{max1} occurs at a mean ± S.D. of 2.0 ±0.9 hours. A second T_{max2} occurs at a mean ± S.D. of 5.5 ± 0.8 hours.

The figures below, reproduced from the Concerta®, Metadate CD®, and Ritalin LA® labels, compare plasma methylphenidate concentration-versus-time profiles from the IR formulations given tid or bid with those following single doses of the multiphasic MR formulations.

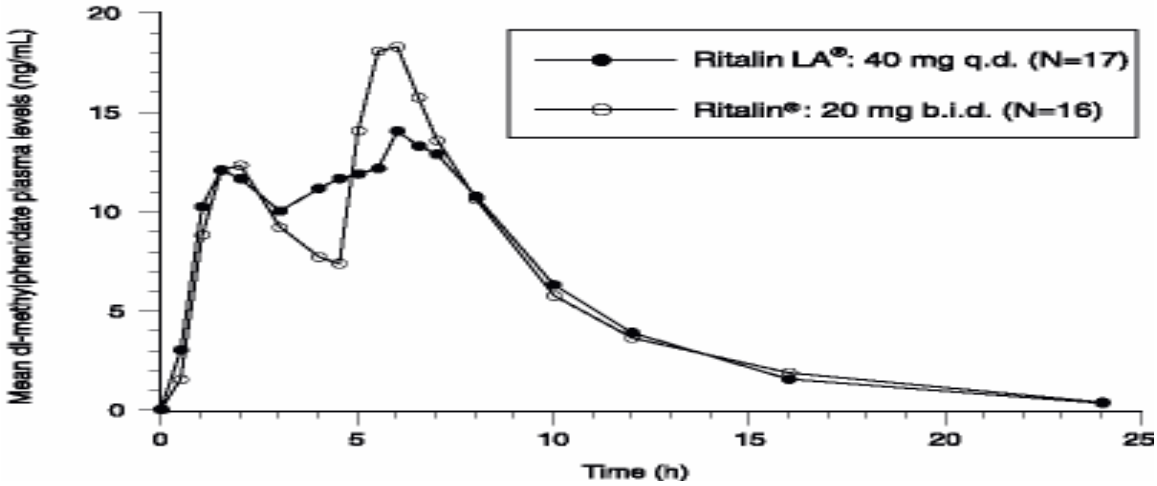
Plasma concentration-versus-time profiles, Concerta® given once daily, compared to IR methylphenidate HCl tid



Plasma concentration-versus-time profiles, Metadate CD® given once daily, compared to IR methylphenidate HCl bid



Plasma concentration-versus-time profiles, Ritalin LA® given once daily, compared to IR methylphenidate HCl bid



Thus, the Concerta®, Ritalin LA®, and Metadate CD® formulations are designed to achieve full efficacy across the day with once-daily administration.

Food (a high-fat breakfast)[23] delays methylphenidate absorption. This effect is observed for the IR formulation and for the some of the multiphasic MR formulations. Food has no effect on the extent of methylphenidate absorption from the multiphasic formulations.

- In healthy male subjects dosed with an IR formulation, the methylphenidate mean ± S.D. T_{max} was 2.00 ± 0.66 hr after an overnight fast and 2.54 ± 0.88 hr when given with food.[24]
- In a study in adult volunteers to investigate the effects of a high-fat breakfast on the bioavailability of a dose of Metadate CD®, the presence of food delayed the early peak by about one hour.
- When Ritalin LA® was administered with a high-fat breakfast to adults, Ritalin LA® had a longer lag time until absorption began and variable delays in the time until the first peak, and the time until the second peak.

Methylphenidate's clinical effects are well-suited for PK / PD analyses. For example, clinical outcome can be assessed using the SKAMP (Swanson, Kotkin, Alger, M-Fynne and Pelham) ratings.[25] SKAMP ratings can be taken at frequent intervals throughout the day (for example, hourly). Thus, the time course of clinical outcome in ADD patients can be related to methylphenidate pharmacokinetics by a PK / PD model. A PK /PD model was developed by comparing the time course of clinical (SKAMP) response to methylphenidate plasma concentrations following dosing with Concerta® or Metadate CD®. The model showed that clinical superiority is expected at any point in time for the formulation with the highest methylphenidate concentration. [26]

As the methylphenidate multiphasic MR dosage forms are designed to achieve both rapid onset of activity and sustained activity throughout the day, OGD suggests that additional metrics may be appropriate to ensure that generic versions are therapeutically equivalent to the corresponding reference products. For these products, the traditional BE metrics may not adequately assess any differences in plasma concentrations that might produce differences in onset of clinical response. As previously stated, two products are deemed bioequivalent if the 90% confidence intervals of the test/reference ratios for C_{max}, AUC_{0-t}, and $AUC\infty$ fall within the intervals of 80-125%. The parameter T_{max} is also evaluated, and, if this parameter differs markedly between the test and reference products, the OGD consults the relevant CDER clinical division to determine whether such differences could result in lack of therapeutic equivalence. However, as seen in the above concentration-time profiles from the labels, for Concerta®, Metadate CD®, and Ritalin LA®, T_{max}, the highest observed plasma concentration, does not occur until methylphenidate from the sustained- or delayed-release portions of the formulations is being absorbed. Thus, the traditional BE metrics (even including T_{max}) will not provide information about whether a generic will provide the same onset of activity as the corresponding reference.

The OGD proposes to use the metrics C_{max}, AUC_{0-3h}, AUC_{3h-t}, and $AUC\infty$ for BE studies for BE studies conducted in fasting subjects, and the metrics C_{max}, AUC_{0-4h}, AUC_{4h-t}, and

AUC∞ for BE studies. These proposals received concurrence from CDER's Division of Psychiatry Products, Division of Pharmacometrics, and Division of Clinical Pharmacology I.

We believe that adding the metrics of $AUC_{0\text{-}3h}$ for the fasting BE studies, and $AUC_{0\text{-}4h}$ for the fed studies will ensure that generic versions of the methylphenidate multiphasic MR products will produce the same onset of response as their corresponding reference products. The reasons for selecting 3 hours and 4 hours for the partial AUCs in fasting and fed studies are as follows:

- For IR methylphenidate products, T_{max} is about 2 hours;
- Food prolongs the T_{max} of IR methylphenidate by about 1 hour;
- The IR methylphenidate T_{max} standard deviation is about 0.5 hour;
- For T_{max}, two standard deviations = 1.0;
- Approximately 95% of observations should fall within two standard deviations of the mean;

Thus, assuming that the T_{max} from the IR portions of these formulations is about 2 hours under fasting conditions and 3 hours under fed conditions, partial AUCs calculated to 3 hours in a fasting BE study and 4 hours in a fed BE study should capture the responses of 95% of the subjects.

We also recommend using $AUC_{3h\text{-}t}$ and $AUC_{4h\text{-}t}$ as BE metrics rather than $AUC_{0\text{-}t}$, in the fasting and fed BE studies, respectively. If a proposed generic and the corresponding reference methylphenidate multiphasic MR product produce the same exposure over this time interval, it is reasonable to assume that they will be therapeutically equivalent with respect to maintenance of the therapeutic response later in the day.

We simulated the outcomes of fasting BE studies of Concerta®, Metadate CD®, and Ritalin LA®, using the metrics of C_{max}, $AUC_{0\text{-}3h}$, $AUC_{3h\text{-}t}$, and AUC∞. We also simulated the outcomes of fed BE studies of these products using the metrics of C_{max}, $AUC_{0\text{-}4h}$, $AUC_{4h\text{-}t}$, and AUC∞. The metrics appear feasible for use in bioequivalence studies. As previously stated, if a particular metric is highly variable, the number of study subjects can be reduced by using alternative approaches, such as replicated study designs for reference-scaled average BE analysis, or sequential study designs.

Appendix D: PK Profile Comparison Metrics

A literature survey was conducted to establish a list of potential metrics (in addition to Cmax and AUC) for comparing PK profiles. The survey was limited to metrics that could be applied to a single dose study. All the metrics identified were evaluated using a set of 60 bioequivalence studies drawn from 5 different drugs (with multiple formulations of each drug). The set of drugs was selected to include bioequivalence studies that had PK profiles with different Tmax, multiple peaks, long plateaus (wide range of Tmax values), and profiles from multiphasic products (those with both IR and ER release mechanisms).

Broad classes of metrics include

- Model Free (Non-Compartment) Methods
- Direct Curve Comparison (DCC) Methods
- Model-based (Deconvolution) Methods

List of Metrics

- **Tmax**
  Tmax is the time of the maximum observed concentration. It is routinely reported and qualitatively examined today. However, the values depend on the scheduled sampling times and there is no consensus on the best statistical method for Tmax comparisons (median values are most commonly reported). It is not well defined in the presence of multiple peaks or when the plasma concentration curve around the peak is flat. Publications disagree on the sensitivity of Tmax to changes in absorption rate.[27,28]
- **Cmax/AUCinf, Cmax/Tmax, Cmax/pAUC[Tmax]**
  These measures attempt to free Cmax from dependence or correlation with the extent of absorption. There are claims in the literature that when the fraction absorbed, F, is highly variable, this measure should perform better than Cmax, when F is low Cmax may be a better measure[29].
- **Partial AUC (pAUC[Tmax])**
  FDA BA/BE guidance suggests pAUC to the median Tmax of the reference product as a measure of early exposure[2]. Literature suggest that pAUC[Tmax] has lower producer risk and higher sensitivity than Cmax or Cmax /AUCinf as a measurement for absorption rate, except for a random lag-time scenario[29].
- **Partial AUC (pAUC[ind Tmax])**
  We also evaluated pAUC from zero to the individual Tmax of the reference product[30].
- **Partial AUC (pAUC[t1-t2])**
  OGD has used partial areas over prespecificed time intervals in several cases. Prespecified intervals appear to have lower variability that pAUC[Tmax]. As the interval time comes closer to zero (for example 0-1.5 or small) variability of this measure increases, primarily due to variation in gastric emptying times. Prespecified intervals include pAUC that use the Tmax of relevant IR products containing the same active ingredient.

- **Area under the moment curve (AUMC)**
  AUMC is the area under the concentration*time curve

$$AUMC = \int_0^\infty tC(t)dt$$

- **Mean Residence Time (MRT)**
  MRT = AUMC / AUC**.** Literature claims that the MRT confidence interval is usually too broad to be applicable to BE studies for drugs with half-life longer than 5 hours[31], and that MRT may be an insensitive measure for BE comparison[32].
- **Peak Occupancy Time (POT-25)**
  Time span over which the concentration is within 25% of Cmax. 25% is specified as a clinically significant difference, thus it could be different for different drugs[33].
- **Tapical**
  The arithmetic mean of the times included in the POT time span.
- **Capical**
  The arithmetic mean of the concentrations included in the POT time span.
- **AUCapical**
  The area under the curve for the POT time span.
- **Half Value Duration (HVD) or POT-50**
  Time span over which the concentration is within 50% of Cmax.
- **F1 curve comparison**
  F1 is a difference factor from the comparisons of dissolution profiles[34]

$$f_1 = 100\frac{\sum_{i=1}^{n}|R_i - T_i|}{\sum_{i=1}^{n} R_i}$$

- **F2 curve comparison**
  The f2 test is the method usually used for comparisons of dissolution profiles[34]. It can be applied either to mean concentration profiles with confidence intervals obtained via a bootstrap or it can be applied to the test and reference curves for each subject and confidence intervals obtained from the individual subject comparisons.

$$f_2 = 50\log\{[1+\tfrac{1}{n}\sum_{i=1}^{n}(R_i - T_i)^2]^{-0.5} \times 100\}$$

  A f2 value of 50 or greater (50-100) is considered as acceptable similarities of two dissolution profiles and corresponds to a 10% difference at each point. To apply the f2 test to a PK profile the Cmax is normalized to 100.
- **DCC Rescigno Index**

$$\xi_j = \left(\frac{\sum_{i=1}^{n} w_i \mid R_i - T_i \mid^j}{\sum_{i=1}^{n} w_i \mid R_i + T_i \mid^j}\right)^{1/j}$$

Ti, Ri are the test and reference concentration at the ith time and wi is a weight chosen to reflect the importance of the sampling time ti. The result is between zero and one, but acceptance limits need to be determined. Values of j equal to 3,1, and 1/3 have been suggested[35].

- **DCC absolute difference (δa)**

$$\delta_a = \frac{2\sum_{i=1}^{n} | R_i - T_i |}{\sum_{i=1}^{n} | R_i + T_i |}$$

Twice the Rescigno index when j=1, weight = R+T.[36]

- **DCC squared difference (δs)**[36]

$$\delta_s = \frac{4\sum_{i=1}^{n} \frac{(R_i - T_i)^2}{(R_i + T_i)}}{\sum_{i=1}^{n} (R_i + T_i)}$$

- **DCC Chinchilli Metric (CM)**

$$\psi = \frac{\sum_{i=1}^{n} 0.5(t_i - t_{i-1})\{T_U(t_i) - T_L(t_i) + T_U(t_{i-1}) - T_L(t_{i-1})\}}{\sum_{i=1}^{n} 0.5(t_i - t_{i-1})\{R_U(t_i) - R_L(t_i) + R_U(t_{i-1}) - R_L(t_{i-1})\}}$$

RL(ti) and RU(ti) are the lower and upper boundaries of the reference region. TL(ti) and TU(ti) are the lower and upper boundaries of the test region. Ψ is the ratio of test region and reference region areas calculated using the trapezoidal rule[35].

RL (ti) = lower acceptance limit * Ri = 0.80 * Ri
RU (ti) = upper acceptance limit * Ri = 1.20 * Ri
TL(ti) = min {Ti, (Ri/Ti)Ri}
TU (ti) = max {Ti, (Ri/Ti)Ri}

- **DCC (ratio weighted)**[36]

$$\rho = \frac{\sum_{i=1}^{n} (R_i + T_i) \times RATIO_i}{\sum_{i=1}^{n} (R_i + T_i)} \qquad Ratio = \max(T/R, R/T)$$

- **DCC (ratio-1 weighted)**[36]

$$\rho_m = \frac{\sum_{i=1}^{n} (R_i + T_i) \times (RATIO_i - 1)}{\sum_{i=1}^{n} (R_i + T_i)} \qquad Ratio = \max(T/R, R/T)$$

- **Partial AUC profile**
  F2 comparison of the cumulative partial areas. At any time point, the curve is the partial area from zero to that time point.
- **Relative AUC profile**
  The contribution of each sampling interval to the relative AUC is calculated[37] and can be compared individually or as a cumulative profile

$$RAUC(j) = \frac{w_j (y_{Tj} - y_{Rj})}{AUC_{\text{Ref}}} \qquad w_i = \frac{(t_{j+1} - t_{j-1})}{2}$$

- **Wagner-Nelson or Loo-Riegelman Deconvolution**
  F2 comparison of the apparent in vivo absorption rate. Assumes that there is a linear elimination process.
- **CAT-model Based Deconvolution**
  Deconvolution of the PK data to a model for in vivo release from the drug product. In vivo release profiles are compared by an F2 test. This requires an assumption of the form of the in vivo release profile and selection of drug disposition model.

Methods for PK metric comparisons used both real and simulated BE data.

- Data Driven
  - A set of drugs, each with multiple BE studies from different sponsors were selected and the full set of metrics were applied to each drug. Confidence intervals and variability were evaluated for each metric.
- Simulation Driven
  - GastroPlus models of the set drugs were constructed and then formulation variations made (change in lag time or in vivo release rate) and the most sensitive PK metric to these variations were identified.

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